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(54) Container comprising a metered dose valve and microparticles of a drug for topical treatment of skin disorders.

(57) Disclosed is a container for delivering a preset amount of a drug for topical treatment of skin disorders.

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ters, and related compounds useful in treating cerebral disorders by incorporating the drug into a biodegradable carrier such as glycolic or lactic acid, albumin, collagen, or gelatin.

U.S. Patent No. 4,962,091, issued October 9, 1990, describes a delivery system for controlled administration of a drug. The system includes a polylactide matrix into which polypeptides are dispersed.

U.S. Patent No. 4,743,583, issued May 10, 1988, discloses a sustained release delivery system for polypeptides. The polypeptides are dispersed in a solution containing a non-aqueous Lewis base and an aqueous Lewis acid to produce an emulsion of microdroplets which are then collected by centrifugation.

U.S. Patent No. 4,659,570, issued April 21, 1987, discloses a stabilized preparation of a polypeptide admixed with chemically modified gelatin.

U.S. Patent No. 5,011,678, issued April 30, 1991, teaches compositions for transmucosal administration of drugs, comprised of a polypeptide-type or other drug, and a biocompatible steroid, in combination with an aerosol propellant.

Canadian Patent Application 2,025,282, published March 14, 1992, describes a method for preparing an aerosol formulation of collagen, optionally containing a carrier such as gelatin and a pharmacologically active agent such as platelet derived growth factor. The formulation is reportedly useful as a wound dressing.

WO 91/16882, published November 14, 1991, discloses a method of preparing a drug-lipid powder composition for water soluble drugs. The powder composition can be administered to the respiratory tract at selected doses by producing an airborne suspension.

WO 91/14422, published October 3, 1991, describes aerosol formulations comprised of a hydrocarbon propellant, a powdered drug, and a dispersing agent. The powdered drug can be a hormone, enzyme, peptide, steroid, antibiotic or other compound, and is prepared in a micronized form such that most of the particles have a diameter of less than about 10 microns. The aerosol formulations are reportedly suitable for dermal, pulmonary or mucosal administration.

U.S. Patent No. 4,892,889, issued January 9, 1990, describes a process for preparing a vitamin powder by spray drying a solution of fat soluble vitamins, gelatin, and water soluble carbohydrates.

U.S. Patent No. 4,734,401, issued March 29, 1988, describes a process for preparing a dried composition of one or more amino acids by spray drying.

U.S. Patent No. 4,233,405, issued November 11, 1980, describes a process for preparing spray dried enzyme compositions. The process involves concentrating a liquid composition of enzyme and water insoluble salts, and spray drying this composition at elevated temperatures.

U.S. Patent No. 3,207,666, issued September 21, 1965, describes a method for forming a dry, free flowing powder containing a highly oxidizable organic substance. A solution of the substance is atomized in the presence of an organic film-forming colloid, an antioxidant, and a carbohydrate to form droplets that serve to protect the oxidizable organic substance from oxidation.

The use of spray applicators for administration of certain drugs that are topically applied is known in the art. For example, Polysporin® brand antibiotic ointment (Burroughs Wellcome, Inc., Research Triangle Park, N.C.) and Decaspray® brand steroid spray (Merck, Sharp & Dohme, Inc., West Point, PA) are both packaged in spray applicators. The problem with these and other spray-type containers is that it is not possible to administer an accurate dose of drug to the targeted skin area; dosage is usually measured by holding the can a certain distance from the skin and spraying the drug for a specified amount of time.

There is a need in the art for spray applicators that deliver to targeted areas accurate and precise doses of drugs used to treat skin disorders such as wounds and surgical incisions.

Accordingly, an object of the invention is to provide a method for dispensing a drug used to treat skin disorders such as wounds and surgical incisions using a spray applicator that delivers a preset dose of the drug to the targeted area of skin.

A further object is to provide suitable formulations of the drug for packaging and dispensing in an aerosol sprayer.

These and other objects will readily be apparent to one of ordinary skill in the art.

SUMMARY OF THE INVENTION

This invention is based on the discovery that formulations of drugs used for treating skin disorders and for wound healing can be prepared and administered in preset doses to deliver an accurate amount of drug to the skin using a spray-type applicator to which is attached a metered dose valve. The invention thus avoids problems encountered with the use of gels, creams, or liquid formulations used for topical application.

In one preferred embodiment, this invention provides a container comprising a metered dose valve and microparticles of a drug used to treat a skin disorder.

In another embodiment, the invention provides microparticles of a drug that have PDGF-like activity.

Methods of Making the Invention

1. Source of the Drug

Any drug used to practice this invention should be soluble in an aqueous medium, and fairly stable at elevated temperatures, *i.e.*, retain at least partial biological activity at temperatures between about 100°C and 150°C. The drug may be organic or inorganic, and may be derived from any natural source, or manufactured synthetically. Drugs may be protein, carbohydrate, lipid, nucleic acid, or may be any other type of organic chemical molecule such as, for example, a heterocyclic, aromatic, or hydrocarbon compound.

This invention contemplates the use of more than one drug in a given microparticle formulation, provided that the drugs, when combined in a single formulation, are chemically and pharmaceutically compatible.

Drugs that are proteins can be obtained by purification of the protein from any endogenous source such as a particular cell-type or tissue of vertebrate animals, invertebrate animals, or plants. Methods for such purification are well known to the skilled artisan, such as those described in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. [1989]). Alternatively or additionally, the protein may be obtained using recombinant DNA technology procedures that are generally well known to the skilled artisan. Where recombinant technology is used to obtain a protein, this invention contemplates the use of biologically active fragments of the protein, as well as mutants of the protein such as insertion, deletion, and/or substitution mutants.

Non-protein drugs can be obtained through any means known in the art, such as by purification from a suitable source, or by chemical or enzymatic synthesis.

Preferred drugs are those that promote wound healing or are useful in treating wounds and surgical incisions, as well as skin disorders such as various skin cancers, dermatitis, rashes, allergic reactions, and various types of acne. Drugs such as steroids, antibiotics, growth factors, including without limitation keratinocyte growth factor (KGF) and platelet derived growth factor (PDGF), are more preferred. The most preferred drug is PDGF-BB in the 119 amino acid sequence form.

2. Source of the Excipient

Th excipi nt can be any pharmaceutically inactive substance, organic or inorganic, that is useful both as a dilution agent and to decrease or prevent undesirable interactions between particles of the drug, such as aggregation, hygroscopic interactions, and the like. Useful excipients are well known in the art (see, for example, *Remington's Pharmaceutical Sciences*, 17th ed., 1985, Mack publishers, Easton, PA). The excipients may be in the naturally occurring form, or may be chemically, enzymatically or otherwise modified. Generally, excipients with a smaller molecular weight (less than about 25,000 daltons for proteins) are preferred, as smaller microparticles can more readily be prepared from them.

More than one excipient may be used simultaneously in a given formulation. The amount of excipient used per unit of drug will depend on the characteristics of the drug, the desired concentration of the drug, and the dose of the drug to be delivered to the target area of skin.

Preferred excipients for use in the invention are various carbohydrates such as lactose, glucose, mannitol or hydroxyethyl starch, or proteins such as human serum albumin, collagen, or gelatin. More preferred excipients are collagen and gelatin, and the most preferred excipient is gelatin hydrolyzed to an average molecular weight of about 20,000 daltons.

3. Sustained Release Formulations

In some cases, it may be advantageous to apply a sustained release formulation of the drug to the target tissue. This may serve to decrease the frequency of applications of the drug. In these cases, certain polymers such as human serum albumin, cellulose, starch or derivatives thereof, or synthetic polymers can be used as a matrix for a sustained release formulation. These polymers must be pharmacologically inert and non-toxic. The desired amount of polymer is added to the formulation. The amount of polymer used will be determined empirically, but will primarily be dependent on its chemical composition, its rate of degradation when applied to skin, the amount of drug present in the formulation, and other similar considerations known to those of skill in the art.

It is known that a drug formulation for wound healing containing the protein epidermal growth factor (EGF) in combination with gelatin is more efficient for promoting wound healing than EGF applied alone. The gelatin is believed to decrease the rate at which the EGF is degraded by proteases present at the wound site(Okumura *et al.*, Pharm. Res. 7:1289-1293 [1990]). By analogy, but without being limited to any one theory, it is believed that PDGF would likely be more efficacious or longer lasting when formulated with gelatin or a comparable matrix. Thus, in the present invention, gelatin would be useful both as an excipient, and to extend the life of PDGF applied to the skin for

fluorocarbon propellant that may be used herein and is not believed to detrimentally affect the ozone layer is 1,1,1-trifluoro-2-fluoro-ethane.

Preferred propellants for use herein are those not containing fluorocarbons that have a vapor pressure between about 15 and 50 psig. One preferred propellant is isobutane. When propellants with vapor pressures outside of this range are used, butane can be added to decrease the vapor pressure, and propane can be added to increase the vapor pressure as is necessary. The amount of propellant used is primarily a function of the desired concentration of drug in the propellant. This in turn is primarily a function of the dose of drug to be applied to the skin per unit of spray administered. Generally, the ratio of drug to propellant will be between about 5-75 mg/ml for PDGF microparticles, and preferably it is about 8-60 mg/ml for PDGF microparticles.

7. Dosage Delivery

A key feature of the present invention resides in the use of a metered dose valve with a fixed volume chamber for precise and accurate delivery of a preset amount of the drug to the targeted skin area. The use of this type of valve is important where the amount of drug applied is critical, such as for wound or surgical incision healing.

Any commercially available metered dose valve may be used to practice the invention, provided that it has a rubber gasket or other type of gasket that is chemically inert with respect to the propellant, the lubricant, and the drug-excipient microparticles. The valve may be of the upright or the inverted type, although the inverted type is preferred for ease of administration. Both preset volume and adjustable volume metered dose valves may be used. However, preset volume valves are preferred, especially the inverted metered dose preset volume valves. The preferred valve for use herein is one that delivers about 100 µl per spray, such as the Valois 20 mm inverted valve (Valois of America Inc., obtained from BLM Associates Inc., Greenwich, CT; type DF 10/100 RC 20mm). Other suitable valves are those manufactured by Bespak, Inc. (Framingham, MA).

Containers used for packaging the microparticle-propellant solution may be made of any material that is inert with respect to the propellant and the drug-excipient microparticles. The container must have an opening of a size that is compatible with the size of the metered dose valve, generally about a 20mm circumference, for convenience of packaging. Preferred containers are those made of aluminum, preferably those having a suitable polymer coating. A preferred container is the Safet Canister 20.9 x 45 x 20 mm with an inside lining made of ONC epoxy phenolic (BLM Associates, Greenwich, CT).

An actuator is affixed to the container-metered dose valve apparatus. The actuator may be any type that is compatible with the metered dose valve selected for use. A preferred actuator is one that has finger rests and a long nozzle. The finger rests provide a means of holding the apparatus comfortably when the apparatus is used in an inverted position for administration, and the long nozzle aids in delivering the drug in a precise manner. This apparatus comprising the container, inverted metered dose valve and actuator is diagrammed in Figure 2.

8. Stability of Formulation

The stability of the formulation over time is important for maintaining the efficacy of the drug. Stability can be monitored using *in vivo* or *in vitro* assays designed to evaluate the activity of the drug. The assays may be conducted by storing a container of the prepared formulation under appropriate temperature conditions for a period of time, and evaluating the biological activity of the formulation at several points during that time.

The invention will be more fully understood by reference to the following examples. These examples should not be construed in any way as limiting the scope of this invention.

EXAMPLE I

1. Preparation of PDGF Microparticles

a. PDGF-Gelatin Microparticles

An aqueous solution of human recombinant PDGF-BB was dialyzed against 10 mM Na acetate, pH 4.0, to remove salts from the solution. The dialyzed solution (50 ml) at a concentration of 2.76 mg/ml PDGF was mixed with a previously filtered solution of 13.66 g of hydrolyzed purified gelatin with an average molecular weight of 20,000 daltons (obtained from Dynagel, Inc., Calumet City, Illinois) in 86.6 ml of water, to yield a final solution of 10 percent by weight of gelatin and 1 percent by weight of PDGF.

b. PDGF-Collagen Microparticles

10 ml of an aqueous solution of 2.038 mg/ml human recombinant PDGF-BB in 10 mM Na acetate, 150 mM NaCl, pH 4.0 was added to 100 ml of a solution of Semed S soluble collagen (Semex Medical Co., Malvern, PA). The collagen was previously prepared at a concentration of 1.0 g/100 ml of 0.1 M acetic acid.

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No noticeable degradation of PDGF was observed either from the Comassie stained gel, or from the Western blot, indicating that the microparticles remained stable over at least a two week period, whether they were stored dry, or in a spray container in the presence of propellant.

Claims

1. A container comprising a metered dose valve and microparticles of a drug for topical treatment of skin disorders.

2. The container of claim 1 wherein the drug possesses human PDGF-like activity.

3. The container of claim 2 wherein the drug is human recombinant PDGF-BB.

4. The container of claim 2 or 3 further comprising an excipient selected from the group consisting of: collagen, gelatin, and carbohydrate.

5. The container of claim 4 wherein the excipient is hydrolyzed gelatin with an average molecular weight of about 20,000 daltons.

6. The container of claim 5 further comprising a propellant and a lubricant.

7. The container of claim 5 that comprises isobutane, isopropyl myristate, and human recombinant PDGF-BB-hydrolyzed gelatin microparticles, wherein the hydrolyzed gelatin has an average molecular weight of about 20,000 daltons.

8. A method of preparing a device to deliver a preset dose of a drug comprising:
   (a) preparing microparticles comprising a drug used to treat a skin disorder;
   (b) packaging the microparticles in a container;
   (c) sealing the container with a metered dose valve; and
   (d) adding propellant to the container.

9. The method of claim 8 wherein the drug has PDGF-like activity.

10. The method of claim 9 wherein the drug is human recombinant PDGF-BB.

11. The method of claim 10 wherein the microparticles comprise human recombinant PDGF-BB and hydrolyzed gelatin with an average molecular weight of 20,000 daltons.

12. The method of claim 11 further comprising adding a propellant and a lubricant to the container.

13. The method of claim 12 wherein the propellant is isobutane and the lubricant is isopropyl myristate.

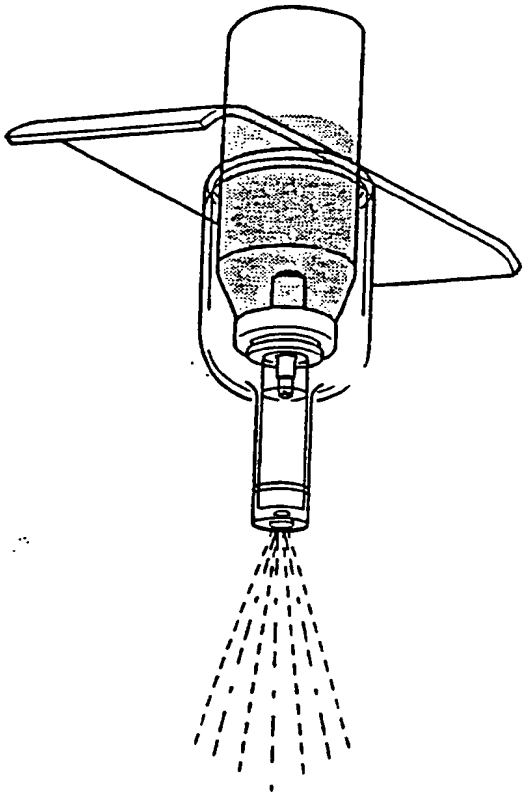

FIGURE 2